REMARKS

Responsive to the Office Action dated May 20, 2003 (Paper No. 22), Applicants respectfully reconsideration of the above-identified application in view of amendments and remarks made herein.

Applicants thank the Examiner for entering the amendments filed on January 27, 2003 upon acceptance of the request for continued examination under 37 CFR 1.114.

Applicants are filing this Amendment and Response together with a Request for a One-Month Extension of Time.

In this Amendment and Response, Applicants have amended claims 69-81, 83-89 and 92 and have added new claim 93. Support for new claim 93 can be found in the specification and the original claims as filed. Claims 69-93 are pending after entry of this Amendment and Response. Further support for the amendments can be found as described in the response sections below. No new matter has been added by virtue of the amendments contained herein.

The Examiner's remarks in the Office Action are addressed below in the order set forth therein.

CLAIM OBJECTION

Claim 92 is objected to because of the informality of labeling as "h)". Applicant have replaced the "h)" with "92." In addition, Applicants have amended this claim to depend from a currently pending claim. Applicants respectfully request, therefore, that the Examiner withdraw this objection.

REJECTION OF CLAIMS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 69-92 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner was not persuaded by the Applicant's previous argument that one skilled in the art would know which amino acid residues are non-phosporylatable, beside the phenylalanine residue used by Applicants.

Applicants respectfully traverse the Examiner's rejections, because by this rejection, the Examiner appears to assume a low skill level for those "skilled in the art." Nevertheless, in order

to expedite prosecution Applicants have amended claims 69, 72, 76, 79, 83, and 87 (the remaining claims being dependent thereon) to cite a conservative substitution for the tyrosine residue. Support for this amendment can be found in the specification at page 17, lines 13 and 14. This amendment narrows the choice of amino acids for substitution to residues which look like tyrosine (*i.e.*, have a ring structure with at least one non-saturated (double) bond, *e.g.*, phenylalanine, tryptophan or histidine). Therefore, one with access to a graphical view of the structures of standard amino acids would be able to select a limited number of amino acids to use as mutant residues and envision a mutant with these residues.

In addition, the Examiner rejects claims 69-92 by contending that a description of the cytoplasmic tyrosine residues of β_3 integrin as tyrosine residues 747 and 759 does not describe "any other cytoplasmic domain tyrosine residues." Applicants respectfully traverse this rejection. A skilled artisan can view Figure 2, which is referenced in the specification at page 17, lines 5-7 and see substitutable tyrosines in the cytoplasmic domain of β_3 integrin. If given any sequence which delineates the cytoplasmic domain of a β_3 integrin, Applicants would expect the skilled artisan to envision substitutable cytoplasmic tyrosine residues by presentation of their three letter (Tyr) or one letter (Y) code and do not believe that Applicants need to describe any other cytoplasmic domain tyrosine residues for β_3 integrin.

In view of these amendments and remarks, Applicants respectfully request that these rejections be withdrawn.

Claims 69-92 also were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and or use the invention. According to the Examiner, the only phenotype for the claimed mice taught by the Applicants in the specification is that they have "non-normal platelet aggregation." In addition, the Examiner writes that the Applicants have failed to provide an enabling disclosure for the claimed mice. Applicants respectfully disagree with the description of at least two definable and measurable phenotypes in the specification:

Tyrosine phosphorylation phenotype: On page 17, lines 17-18 and page 18, lines 15-16, Applicants wrote that the substituted residues will be unable to be phosphorylated (unlike the wild type tyrosine residues which are phosphorylatable). One skilled in the art will know how to measure tyrosine phosphorylation. In addition, Applicants incorporate by reference U.S. Patent

No. 6,210,913 (as amended on page 1 of the specification, updated from the original incorporation of it as a pending U.S. Application No. 08/734,607), which further enables this phenotype by describing at least one method for assessing phosphorylation of tyrosines on β_3 integrin.

Platelet aggregate phenotype: In addition to the statements about this phenotype of record in response to the previous Office Action (Paper No. 17, filed January 27, 2003) and acknowledged by the Examiner as described above, contrary to the Examiner's assertion, Applicants do further describe this phenotype. On page 16, lines 1-2, Applicants state that the mutant mice will "be defective in thrombotic responses, where the formation of very large platelet aggregates is required." A consultation of the meaning of the term "defective" in a standard dictionary (*The American Heritage Dictionary*, Office Edition, Houghton Mifflin Company, Boston, 1983) explains "defective" as "having a defect," and "defect" as "lack of something necessary and desirable." From the sentence in the specification, it is clear that the "lack of something" would be the "very large platelet aggregates." One skilled in the use of models of thrombosis in mice would be enabled for practicing the claimed invention.

Therefore, as Applicants have clearly taught more than one phenotype for the claimed transgenic mice and as stated in response to an earlier office action, have provided a post-filing reference confirming at least one phenotype, Applicants respectfully request withdrawal of this rejection.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 69-73, 77, 80, 83-86 and 89 are rejected under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claim 69 is rejected, because, according to the Examiner, it is vague and indefinite by citing that the mouse comprises a mutant GP IIIa gene and as written would encompass a chimeric mouse or a xenograft mouse, as well as the claimed transgenic mouse. Applicants have amended claim 69 (and dependent claims 70, 71 and 75) to clarify the claimed mouse as a "chimeric" mouse. Support for this amendment can be found in the specification, for example at page 15, lines 17-18.

A further rejection of claim 69 is that it is unclear whether the gene with the replaced tyrosine is the mutant GP IIIa or the wild type GP IIIa. Applicants have amended claim 69 to clarify that the mutant gene has a substitution for the wild type tyrosine.

In view of these amendments, the Examiner should withdraw these rejections.

Claims 70, 73, 77, 80, 84, and 89 are rejected as being vague and indefinite. The Examiner states that the recitation of tyrosine residue 747 and 759 is unclear because the numbering would depend upon the sequence. Applicants respectfully direct the Examiner to the specification at page 15, lines 6-7 as stating that tyrosines 747 and 759 are the "two tyrosines in the cytoplasmic domain" and to Figure 2, which illustrates this. In addition, in Example 1 at pages 19-20, Applicants provide references to a partial mouse GP IIIa amino acid sequence and a complete human sequence. Applicants also note that the cytoplasmic domain of the mouse sequence is identical to that of the human sequence. Applicants further provide numerical reference points of nucleotides of the murine GP IIIa gene. Based on these amino acid and nucleic acid reference points, Applicants believe that recitation of tyrosine residue numbers is definite.

A further rejection of claims 70, 73, 77, 80, 84, and 89 is that it is unclear whether the gene with the replaced tyrosine is the mutant GP IIIa or the wild type GP IIIa. Applicants have amended claims 70, 73, 77, 80, 84, and 89 to emphasize the mutant and wild type entities in the claims and clarify that the mutant gene has a substitution for the wild type tyrosine.

In view of these amendments, the Examiner should withdraw these rejections.

Claim 72 is rejected, because, according to the Examiner, it is vague and indefinite by citing that the mouse comprises a mutant GP IIIa gene and as written would encompass a chimeric mouse or a xenograpft mouse, as well as the claimed transgenic mouse. Applicants have amended claim 72 (and dependent claims 73 and 74) to clarify the claimed mouse as a "chimeric" mouse. Support for this amendment can be found in the specification, for example at page 15, lines 17-18. In view of these amendments, the Examiner should withdraw this rejection.

Claim 83 is rejected as being incomplete. To support this rejection, the Examiner explains that more than ES cells are required to generate a mouse, which further requires

introduction into a surrogate mother. Applicants respectfully disagree, but in order to expedite prosecution, have amended claim 83 (84-86 dependent thereon) to add the additional step of injecting the mutant ES cells into a blastocyst. Support for this amendment can be found in the specification for example at page 8, lines 20-22 and page 15, line 17. Applicants contend that a blastocyst with mutant cells generates a mutant mouse. Furthermore, the specification at page 15, line 16, states that the method to obtain such mutant mice are "standard methods" and thus do not need to be recited in the claims. Claim 86 was amended to relabel the steps to account for the additional step in claim 83. In view of these amendments and remarks, Applicants respectfully request that the Examiner withdraw this rejection.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 102

Claims 75 and 82 were rejected under 35 U.S.C. § 102(b) as being anticipated by Zhou *et al.* (Blood 89:1551-1559). The Examiner states that Zhou isolated platelets which do not require a phenotype. The Examiner further states that neither the mouse of the antecedent claim 69, a potentially chimeric or xenograft mouse, nor the mouse of claim 76, a potentially heterozygous mouse, recites a phenotype, therefore the resulting platelets could be wild type platelets.

Applicants respectfully traverse this rejection. However, in order to expedite prosecution, Applicants have amended claims 69 and 76 (claims 75 and 82 dependent thereon). The amendments recite that the claimed mouse have reduced or absent phosphorylation of GP IIIa (β_3) protein compared to wild type mouse. Support for this amendment can be found, for example as described above for the tyrosine phosphorylation phenotype and at page 18, lines 9-10. Applicants point out that while some platelets isolated from the mouse may have the wild type GP IIIa (β_3) protein, the mouse, which is the source of the platelets, will have the phenotype of at least reduced phosphorylation of GP IIIa (β_3) protein. This phenotype is not taught by Zhou, thus, Applicants request that this rejection be withdrawn.

CONCLUSION

The foregoing amendments and remarks are being made to place the Application in condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims because, in view of these amendments and remarks, Applicant respectfully submits that the objection and rejections of the claims under 35 U.S.C. § 112 and 35

U.S.C. § 102 are overcome. Applicants believe that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned. If the Examiner disapproves of Applicants's amendments and remarks in this response, Applicants request a prompt mailing of a notice to that effect.

This paper is being filed timely as a request for a one month extension of time is filed concurrently herewith. No additional extensions of time are required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

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